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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,887	12/11/2001	Geoffrey W. Krissansen	8654/2072	2382

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,887	KRISSANSEN ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-47* is/are pending in the application.

4a) Of the above claim(s) *10-11,15,18,19,23,26,27,31,34,35,39,42 43,and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,12-14,16,17,20-22,24,25,28-30,32,33,36-38,40,41 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

The request filed on 6/15/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10014887 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 5 and 48-55 have been cancelled. Claims 1-4 and 6-47 are pending. Claims 10-11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43, and 47 have been withdrawn previously. Claims 1-4, 6-9, 12-14, 16-17, 20-22, 24, 25, 28-30, 32, 33, 36-38, 40, 41, 44-46 are under consideration.

Previous final Office Action dated 12/7/05

Priority: Applicants state in the response filed 6/15/06, "filed herewith is a certified copy of NZ336259". The Office has not received such copy. Therefore, the priority on 6/14/2000 for this application granted in the prior Office action dated 12/7/05 is maintained until the Office will have received a certified copy of NZ336259.

Election/restriction: Withdrawal of claims 15. 23. 31, 39, and 47 for examination is maintained as stated in the prior office action dated 12/7/05. Applicant requests rejoinder of the claims when independent claims 1-4 and 6 are allowable. As stated in the election/restriction, Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). Therefore, if independent claims 1-4 and 6 are allowable, the Office will consider rejoin the withdrawn claims 15. 23. 31, 39, and 47 at that time.

The rejections in the previous Office action, dated 12/7/05, including rejection of claims under 35 U.S.C. 112 first paragraph and under 35 U.S.C. 103 are withdrawn. If any rejection/objection is maintained, it will be stated again below.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 5/16/03, 1/23/03, 5/9/02 are/is considered by the examiner and initialed copies of the PTO-1449 are enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As drawn to scope of enablement

Claims 1-4, 6, 8, 12-14, 16, 20-22, 24, 28-30, 32, 36-38, 40, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a mammal with advanced or large tumor burdens, or potentiating the activity of T-cell to eradicate an advance or large tumor comprising the administering B7.1 in combined with DMXAA, and being enabling for a method of treating a tumor with a cytokine comprising IL-2 plus analogues of XAA disclosed in the art, does not reasonably provide enablement for the method using any CAM in combined with any tumor restricted agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are broadly drawn to a method of treating for a mammal with advanced or large tumor burdens, or for a patient with cancer, or potentiating the activity of T-cell to eradicate an advance or large tumor comprising the administering any T-cell co-stimulating cell adhesion molecule (CAM) with any tumor growth-restricted agent.

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The method objective of claims is treating tumor with a CAM plus a tumor restricted agent to effectively eradicating an advanced or large

tumor. Thus, it would be expected that one of skill in the art would be able to eradicate an advanced tumor or large tumor without undue experimentation by using the claimed method.

The specification teaches the CAMs in the method include B7.1, B7.2, VCAM-1, MAdCAM-1 and ICAM-1 etc (para 37-40) and the tumor restricted agent in the method include analogs of XAA and FAA, cytokine IL-12, antisense to VEGF, FLt-1 etc (pare 50-58). However, the only combined therapy of a CAM and a tumor growth restricting agent used for treating a tumor in the application is administering B7.1 in combination of DMXAA to mice to eradicate tumors (figure 2, 5, 8, 12, paragraph 98). The specification does not provide a method of using any other CAM in combination with any other tumor restricted agent successfully treating or eradicating any large or advanced tumors. The specification does not provide enough direction or guidance for the claimed method of the combination therapy with any CAM combined with any tumor restricted agent encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would use the claimed method without experimentation.

One skilled in the art recognizes that the search for combinations of drugs (each has less effect when it is used alone) exerting a combined effect requires a great deal of empirical testing of agents known to have anti-cancer properties or that may augment an agent having anti-cancer properties (Gerson et al, WO03/070234, page 2, lines11-14). In addition, not all the analogue of XAA has a tumor restricted function, Futami et al., (J of Immunotherapy, vol 12, 247-255) indicates that 7-methyl-XAA, a analogue of XAA, self, or combination with IL-2 has not synergistic activity in suppression of tumor growth (page 252-253, col 1). Thus, it would be undue experimentation to test two agents in combination in order to determine whether one skilled in the art could use them together for treating a large or advanced tumor.

Since the specification does not provide claimed method for using any other CAM except B7.1 in combination with any other tumor restricted agent except DMXAA, one skilled in the art would not know how to use the claimed method to treat large or advanced tumor comprising administering any CAM combined with any tumor restricted agent.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to claimed method, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention. If Applicants has any objective evidence contrary to the rejection, Applicant is invited to submit it to the Office for reconsideration.

As drawn to written description

Claims 1-4, 6, 8, 12-14, 16, 20-22, 24, 28-30, 32, 36-38, 40, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of treating for a mammal with advanced or large tumor burdens, or for a patient with cancer, or potentiating the activity of T-cell to eradicate an advanced or large tumor comprising the administering any T-cell co-stimulating cell adhesion molecule (CAM) with any tumor growth-restricted agent.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification teaches that CAMs in the claimed method include B7.1, B7.2, VCAM-1, MAdCAM-1 and ICAM-1 etc (para 37-40). The specification teaches that the tumor growth restricting agents in the method including analogs of XAA and FAA, cytokine IL-12, antisense to VEGF, FLt-1 etc (pare 50-58) The specification, in the result section, teaches a method of treating tumor alone with CAMs, B7.1, B7.2, ICAM-1, or Vcam or alone with analogues of XAA as tumor restricted agent (paragraph 74-75, figure 1-2). However, the only combined therapy of a CAM and a tumor growth restricting agent for treating a tumor disclosed in the specification is administering B7.1 in combination of DMXAA in mice to

eradicate tumors (figure 2, 5, 8, 12, paragraph 98). The specification does not provide a method of using a CAM other than B7.1 in combination with any other tumor restricted agent successfully treating or eradicating any large or advanced tumors. The specification does NO more than a description of the combination therapy with any CAM combined with any tumor restricted agent encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The claimed methods depend on combination therapy of CAM and tumor restricted agent to eradicate an advanced or large tumor. Without experimentations for testing the specific CAM in combined with a specific tumor restricted agent in eradicating a large or advanced tumor successfully, one skilled in the art is not convinced the method would be successful for treating a large or advanced tumor and not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness

Claims 1-4, 6-9, 12-14, 16-17, 20-22, 24, 25, 28-30, 32, 33, 36-38, 40, 41, 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Futami et al., (J of Immunotherapy, vol 12, 247-255) in view of Olsson et al., (International Immunology, vol 10, page 499-506).

The claims are drawn to methods of treating a patient with cancer or potentiating the activity of tumor restricted agent comprising an analogue of Xanthenone-4 acetic acid (XAA) or 5, 6 dimethylxanthenone-4-acetic acid (DMXAA) for treating cancer by administering T-cell co-stimulatory cell adhesion molecule (CAM) comprising B7.1, CD80 antigen, in conjunction with analogue of XAA.

Futami et al., teach a method of treating tumor by analogues of XAA comprising 5-methyl XAA in conjunction with a T-cell stimulating molecule, IL-2. Futami et al., teach that the activities of XAA analogues can be potentiated by recombinant IL-2 in treating a tumor. Futami et al., teach a method of treating cancer by administering a subject both reagents or administrating two reagent at different time (page 249, column 1-2 and page 251, column 1). Futami et al., also teach the analogues of XAA alone or IL-2 alone is not as effective as combined therapy for treating a mice bearing a tumor (figure 2-4).

Futami et al., do not teach that treating cancer with analogue of XAA in conjunction with a CAM.

Olsson et al., teach Human IL-2 is induced by CD80 (B7.1, a CAM molecule) in cancer cells and T cells (entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method to eradicate any advanced or large tumor by administering analogues of XAA in combination of CAM comprising B7.1(CD80) with the expected result for cancer treatment. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to potentate the activity of single reagent for cancer treatment by a second reagent. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Olsson et al., with the teaching of Futami et al., to treat cancer by administering a patient with a CAM and analogues of XAA comprising DXMAA because Futami et al., have suggested that IL-2 induced by B7.1 and analogues of XAA have a synergy effect for eradicating established tumor when they are administered together and Olsson et al., have shown that IL-2 is induced by a CAM, B7.1. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method by administering CAM and analogues of XAA together, administering one reagent prior to another, or administering additional analogues of XAA for cancer treatment.

Applicants argue in the Remark filed 6/15/06 that the prior art references fail to provide suggestion or motivation to modify the reference or combine the reference teaching. Applicant also argue that there is no teaching or suggestion in either of the references that treatment of XAA and A CAM (B7.1) will produce a synergistic effect in eradicating advance or large tumors. In response to this argument, first, Applicants do not claimed a method of combination therapy has the synergistic effect. Second, although the references do not suggest modification of the method by combining a CAM (B7.1) with analogues of XAA, the method and evidence disclosed by the reference suggests that the agent is replaceable because Olsson et al., have suggested that IL-2 is induced by a CAM, B7.1, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to replace IL-2 with B7.1 in the method taught by Futami et al., for treating tumor. Therefore, it would have been prima facie

obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method by replacing IL-2 with CAM (B7.1) for tumor treatment.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER